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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/147,036	12/15/1998	JOCHEN MAURER	P564-8019	1165

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/147,036	MAURER ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,41 and 43-59* is/are pending in the application.

4a) Of the above claim(s) *4-8 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9-19,41,43-53 and 55-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's after final amendment filed October 22, 2003 has been entered. Claim 1 has been amended.

2. Upon further review and reconsideration, the finality of the rejection of the last Office Action, mailed April 22, 2003 is withdrawn and new rejections are set forth below:

Rejections Withdrawn

3. In view of Applicant's amendment and response the following rejections set forth in the Office action mailed October 15, 2002 have been withdrawn:

a) Rejection of claims 1-3, 9-10 and 15-19 under 35 U.S.C. 102(b), pages 2-4, paragraph 4 of the previous Office action.

b) Rejection of claims 1-3, 9-10, 15-16, 41, 43-53 and 55-59 under 35 U.S.C. 103(a), pages 4-7, paragraph 5 of the previous Office action.

c) Rejection of claims 1-3, 9-19, 41, 43-53 and 55-59 under 35 U.S.C. 103(a), pages 7-9, paragraph 6 of the previous Office action.

New Grounds of Rejection

Specification

4. This application also fails to comply the requirements of 37 C.F.R. 1.821-1.825 because it contains nucleic acid sequences that are not identified. For example, the sequences in figures 6-24 are not identified. Appropriate sequence identifiers should be used to comply with sequence rules. The sequences in the specification should match the sequence listing and computer readable form (CRF) submitted with the application.

5. The specification is objected to for the following informalities: because of the genus and species of organisms should be underlined or italicized. See for example, page 5, line 15. The entire specification should be reviewed for these types of informalities. Correction is required.

Claim Objections

6. Claims 1-3 and 9-19 are objected to for the following informalities: Claim 3 recites the name of organisms that should be underlined or italicized. Claim 3 also recites Aida protein which should be capitalized.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit

7. Claims 1-3, 9-19, 41 and 43-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-3, 9-19, 41 and 43-59 are drawn to a process for presenting passenger peptides or polypeptides on the surface of gram-negative bacteria, a process of obtaining a library of bacteria expressing a variant population of surface-exposed passenger peptides or polypeptides, a recombinant vector and a recombinant gram-negative host bacterium.

Because it is not clear that cell lines possessing the properties of a gram-negative host cell comprising a variant of the *E. coli* transporter domain of the AIDA protein are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the claims require the use of a suitable deposit for patent purposes a deposit in a public repository is required. Without a publicly available deposit of the above gram-negative host cell, one of ordinary skill in

the art could not be assured of the ability to practice the invention as claimed. Exact replication of the cell line is an unpredictable event.

Applicant's referral to the gram-negative host cell in the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met. If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by the International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application. These requirements are necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in the public repository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the repository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;

2) The name and address of the depositor;

3) The date of deposit;

4) The identity of the deposit and the accession number given by the depository;

5) The date of the viability test;

6) The procedures used to obtain a sample if test is not done by the depository; and

7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit. If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the gram-negative host cell described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d.1216, 227 USPQ (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Enablement

8. Claims 1-3, 9-19, 41, 43-53 and 55-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for presenting passenger peptides or polypeptides on the surface of gram-negative host bacteria, wherein the transporter domain is an Adhesin Involved in Diffuse Adherence (AIDA) protein of *E. coli*, does not reasonably provide enablement for process for presenting passenger peptides or polypeptides on the surface of gram-negative host bacteria, wherein the transporter domain is a variant of the AIDA protein of *E. coli* or variant thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches that the C-terminal domain of the AIDA protein, the AIDA autotransporter serves as a membrane anchor for the presentation of recombinant antibody domains on the surface of gram-negative bacteria (page 13). The specification teaches in experimental examples 1 and 2 that the natural surface protein of *E. coli* was chosen for the invention, which was the AIDA protein of *E. coli* (page 33). The specification teaches that the sequence of this protein is known (page 33).

The prior art, for example, Benz et al (*Infection and immunity, May 1989, p. 1506-1511)* teach that the biochemical properties of ADIA are still under investigation (page 1511). Benz et al (*Molecular Microbiology, 1992, 6(11), 1539-1546)* teach that the

adherence mechanisms of enterpathogenic *E. coli* to epithelial cells is not understood (see the Summary).

The instant specification does not teach or define a structure for variants of the AIDA protein. There is no guidance provided as to which amino acids can be added, deleted or substituted and the AIDA protein would retain its biological function. The scope of the claims is not commensurate in scope with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity/utility requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be

made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some polypeptides is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such polypeptides.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting variants of the AIDA protein having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use variants of the AIDA protein in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-3, 9-19 and 41, 43-53 and 55-59 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Correction and/or clarification is required.

a) Claim 1 recites the term "step" on lines 15-18 of the claim. It is unclear as to which steps of the claimed process are method steps? The term "step" should be recited before each process step, for example before a) and b) of the claimed method. The term "step" should be deleted from lines 15-18.

b) Claim 1 recites "under conditions". It is unclear as to what applicant is intends?

c) Claims 9 and 10 recite "wherein one or more peptides". It is unclear as to which peptides of claim 1, applicant is referring? f)

d) Claims 14 and 41 recite "capable of", it is unclear as to what applicant is referring?

e) Claim 16 recites "variant passenger peptides" and "a mixture of non-variant passenger polypeptides", it is unclear as to what applicant is referring?

f) Claim 18 recite "comprising different transporter domains and different passenger proteins". It is unclear as to which different transporter domains and different passenger proteins, applicant is referring?

g) Claim 19 recite "a library of variant peptides or polypeptides". It is unclear as to what "a library of variant peptides or polypeptides" applicant is referring? Correction is required.

h) Claim 41 does not recite a step h).

i) Claim 45 it is unclear as to what method steps Applicant is referring? For example, steps g) and h) do not recite process steps.

j) Claims 55 and 57 recite the term "step". It is unclear as to which steps of the product claims are method steps? The recitation step b) and step e) in the claimed product are not method steps but components of the claimed product.

Status of Claims

10. No claims are allowed.

Conclusion

11. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Vanessa L. Ford
Biotechnology Patent Examiner
February 16, 2004

NITA MINNIFIELD
PRIMARY EXAMINER
2/19/04